Fortnightly Review

Evaluating fever in travellers returning from tropical countries

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With increasing numbers of travellers worldwide, doctors are often faced with the dilemma of a febrile patient who has recently visited a tropical country. Fever is an important and common presentation of tropical diseases and may sometimes be the only manifestation of a serious illness. Diagnosis is often difficult because of the many diagnostic possibilities, signs, and symptoms which may often be non-specific and because of doctors' unfamiliarity with many tropical diseases. A stepwise and rational approach to febrile travellers will allow for correct diagnosis and optimal management in most patients.

When evaluating fever in travellers who have returned from a tropical country, the doctor must first determine if the patient has a tropical disease or an illness that is found in non-travellers as well. If a tropical infection is suspected doctors should consider which illnesses are potentially fatal, which are treatable, and which infections are potentially transmissible and may therefore pose a public health risk. Such an approach needs a clear understanding of tropical illnesses and their presentation and epidemiological background. A working differential diagnosis can be formulated from a complete history, physical examination, a knowledge of the most common diseases affecting travellers and of the incubation periods of these diseases, and appropriate laboratory investigations.

Summary points

- Fever in the returned traveller may represent a tropical infection or an illness common to non-travellers such as pneumonia or urinary tract infection
- The most common tropical infections are malaria, dengue fever, hepatitis and enteric fever; of these, malaria is by far the most important
- Malaria is potentially fatal and may progress rapidly; it should be ruled out as soon as possible in all febrile patients who have travelled recently in the tropics
- Useful diagnostic points include travel history, travel itinerary, vaccination and prophylaxis history, an assessment of incubation period, and specific exposure history
- Initial investigations include thick and thin blood films for malaria; a complete blood count; liver function tests; urine analysis; culture of blood, urine, and stool; and arbovirus serology

Aetiology of fever

Table 1 lists the final diagnosis in patients with fever after travel to a tropical country as reported in two studies.[1,2] Clearly, all febrile patients with a history of recent travel do not necessarily have a tropical infection; an appreciable proportion will have infections that are common in non-travellers, such as an upper respiratory tract infection, community acquired pneumonia, and urinary tract infection.[1,2] The most common tropical infections in travellers who have returned from a tropical country include malaria, enteric fever, viral hepatitis, and dengue fever. Malaria is by far the single most important cause of fever in a recent traveller from the tropics. As falciparum malaria has the potential to be rapidly fatal and is curable with appropriate treatment, this diagnosis must be a primary consideration in such patients. Although a discussion of haemorrhagic fevers is beyond the scope of this review, clinicians must always consider the possibility of these potentially dangerous infectious diseases, particularly if the patient has been in a rural, endemic area and becomes ill within 21 days of his or her last exposure.

Table 1—*Aetiology of fever after travel to tropics. Values are percentages of patients*

Diagnosis	MacLean *et al*[1] (n=587)	Doherty *et al*[2] (n=195)
Malaria	32	42
Hepatitis	6	3
Respiratory infection*	11	2·5
Urinary tract infection	4	2·5
Dengue fever	2	6
Enteric fever	2	2
Diarrhoeal illness	4·5	6·5
Epstein-Barr virus	2	0·5
Pharyngitis	1	2
Rickettsia	1	0·5
Amoebic liver abscess	1	0
Tuberculosis	1	2
Meningitis	1	1
Acute HIV infection	0·3	1
Miscellaneous	6·3	5
Undiagnosed	25	24·5†

*Includes upper respiratory tract infection, bronchitis, and pneumonia.
†Includes presumed viral and non-specific infections.

Approach to diagnosis

Determination of travel history, incubation period, unique exposures, and vaccination history accompanied by a background knowledge of the clinical presentation and distribution of tropical infections will allow for a rational approach to investigation and management. In this regard, one of the most useful and

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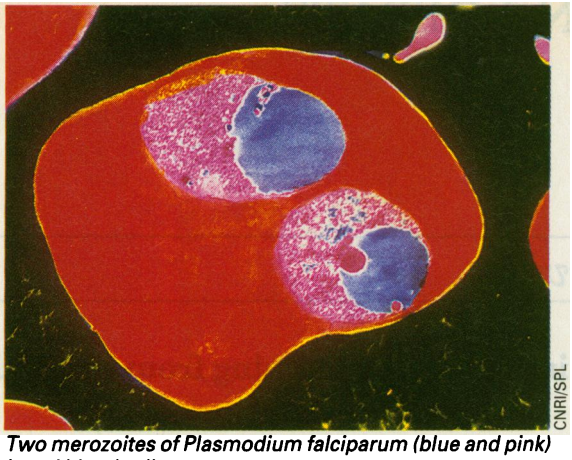


Two merozoites of Plasmodium falciparum (blue and pink) in red blood cell

practical sources of information on the distribution and differential diagnosis of infectious diseases acquired globally has been published recently.[3]

HISTORY

An accurate history will allow the doctor to formulate an appropriate differential diagnosis and help to guide initial investigations. In addition to questions about specific presenting symptoms and medical history (including a drug history), several important travel related topics should be addressed. In addition to questions about possible exposures to infectious agents, the following should be asked.

(1) Where did you travel and what were your arrival and departure dates?
(2) Did you travel in urban or rural areas?
(3) What was the purpose of your travel?
(4) What vaccinations did you receive?
(5) Were you taking malaria prophylaxis? If so, which drug did you take, did you take it appropriately, and are you still taking it?

TRAVEL HISTORY

An accurate travel history will help to determine the duration and likelihood of exposure to infectious disease and whether the illness fits a known incubation period. Countries visited and duration of stay at each location should be determined. Several diseases have a worldwide distribution among tropical countries. These include malaria, dengue fever, hepatitis, enteric fever, tuberculosis, HIV, and amoebic liver abscess.[4-6] Other infections are generally limited to certain geographical areas. For example, diseases restricted to certain locations in Africa include yellow fever, African trypanosomiasis, and haemorrhagic fever due to Lassa, Ebola, or Marburg viruses.[4-6] Inquiring about living conditions during travel is also useful. Generally, travellers to rural areas have a higher risk of acquiring tropical infections than travellers who stay in urban centres or whose accommodation is primarily in first class hotels. Activities such as hiking and backpacking in more remote areas increase the chances of exposure to vectors such as ticks, mites, and flies and to fresh water infested with snails containing schistosomes.

VACCINATION AND PROPHYLAXIS

Vaccination against yellow fever, hepatitis A, and hepatitis B is extremely effective and makes subsequent infection with these agents very unlikely.[6-8] Vaccination against typhoid or use of immunoglobulin for prevention of hepatitis A, however, is only 70-80% protective, and therefore such infections should still be considered even among those who have been immunised.[8,9] Childhood immunisations against diseases such as polio and measles may not be protective if boosters have not been given. It is important to remember that foreign born nationals may not have received routine childhood vaccinations.

With the progressive spread of drug resistant *Plasmodium falciparum* malaria globally and the recent emergence of chloroquine resistant *P vivax*, no prophylactic regimen is 100% protective. Chloroquine chemoprophylaxis remains effective only in parts of the Middle East, Haiti, and Central America.[10] While mefloquine offers substantial protection, resistance is present in areas of South East Asia.[10] Other regimens, such as chloroquine plus proguanil, are even less effective, providing only 60-70% protection in Africa, a hyperendemic malarious area. In addition, poor compliance with antimalarials among travellers has been a well documented cause of failure of chemoprophylaxis.[11] For these reasons malaria continues to be an important diagnostic consideration in febrile patients who have been receiving malaria prophylaxis.

INCUBATION PERIOD

A precise travel history will usually allow the doctor to determine the approximate incubation period for the presenting illness. In many cases this will help to eliminate several potential infections and focus the differential diagnosis. The box shows the incubation periods for selected tropical infections. Fever beginning more than three weeks after return from an endemic area, for example, effectively rules out arboviral infections (including dengue fever), rickettsial infections, and viral haemorrhagic fevers (due to Ebola, Lassa, and Marburg viruses).[4] Falciparum malaria generally has an incubation period of 8-40 days, while infection with *P vivax* or *P ovale* may not occur for several months or years after exposure owing to the presence of dormant hypnozoite stage parasites in the liver.[12] Antimalarial suppressive drugs may further prolong the incubation period for all types of malaria. Although some infections have variable incubation periods—such as typhoid fever, in which incubation may range from 3 days to 60 days[13]—accurate determination of the incubation period will often prove very helpful.

HISTORY OF SPECIFIC EXPOSURE

A history of specific exposure should be sought from

Typical incubation periods for selected tropical infections*

Short (<10 days)
Arboviral infections (including dengue fever)
Enteric bacterial infections
Typhus (louse borne, flea borne)
Plague
Paratyphoid
Haemorrhagic fevers

Medium (10-21 days)
Malaria
Typhoid fever
Scrub typhus, Q fever, spotted fever group
African trypanosomiasis
Brucellosis
Leptospirosis

Long (>21 days)
Viral hepatitis
Malaria
Tuberculosis
HIV
Shistosomiasis (Katayama fever)
Amoebic liver abscess
Visceral leishmaniasis
Filariasis

*Adapted from Strickland[4]

Specific exposures and tropical infections

Exposure	*Infection or disease*
Raw, undercooked or exotic foods	Enteric infections, hepatitis, trichinosis
Drinking untreated water; milk, cheese	Salmonellosis, shigellosis, hepatitis, brucellosis
Fresh water swimming	Schistosomiasis, leptospirosis
Sexual contact	HIV, syphilis, hepatitis, gonococcaemia
Insect bites	Malaria, dengue fever (mosquitoes); typhus, Crimean-Congo haemorrhagic fever, borreliosis, tularaemia (ticks); Chagas' disease (reduviid bugs); African trypanosomiasis (tse tse flies)
Animal exposure/bites	Rabies, Q fever, tularaemia, borreliosis, viral haemorrhagic fevers, plague
Exposure to infected persons	Lassa, Marburg, or Ebola viruses; hepatitis; typhoid; meningococcaemia

patients (box). Eliciting unique exposures may help to point to a specific diagnosis—for example, a patient with a history of a tick bite presenting with fever, rash, regional lymphadenopathy, and a painless skin eschar suggests tick typhus due to rickettsia. Recently, a group of 15 travellers developed acute schistosomiasis (Katayama fever), presenting with a constellation of symptoms including fever, myalgias, headache, gastrointestinal symptoms, and eosinophilia two to eight weeks after swimming in fresh water lakes in West Africa.[14] Traditional cultural restraints on sexual behaviour may not be present during travel, and therefore a history of sexual exposure is important when evaluating the febrile traveller. A history of unprotected sexual intercourse, for example, may point to the diagnosis of an acute retroviral syndrome with HIV, which often manifests as fever and a mononucleosis-like illness one to six weeks after exposure.[15] As many tropical illnesses may have overlapping and non-specific signs and symptoms, a unique exposure is often the only clue to the correct diagnosis.

FEVER PATTERN

Fever patterns are rarely diagnostic but can be helpful in certain infections. Dengue virus infection, for example, typically presents with two febrile periods separated by an afebrile interval of one to three days (saddle back fever).[16,17] Fevers that occur at regular intervals of 48-72 hours are virtually pathognomonic of *P vivax*, *P ovale*, or *P malariae* infections.[12] Although untreated typhoid fever classically presents with a continuous fever associated with relative bradycardia, almost any fever pattern can develop.[13]

PHYSICAL EXAMINATION

Physical findings in many tropical infections are non-specific, and considerable overlap exists. Certain signs, however, will help to narrow the differential diagnosis. The box shows the physical findings and the tropical illnesses with which they are most often associated. A maculopapular rash may be seen in several diseases, including dengue fever, HIV, rickettsial infections, hepatitis B, leptospirosis, and brucellosis. A more specific skin finding is an eschar, a painless ulcer with a black centre and erythematous margin, which is associated with tick or scrub typhus.[1] Rose spots, present in typhoid fever, are transient crops of 2-3 mm pink macules on the chest or abdomen that blanch with pressure.[13] Splenomegaly or lymphadenopathy is sufficiently common in many tropical illnesses that their presence is not usually diagnostic. Lymphadenopathy, however, is unusual in malaria, and its presence suggests an alternative diagnosis.[11]

Possible physical findings in selected tropical infections

Physical finding	*Infection or disease*
Rash	Dengue fever, typhoid, typhus, syphilis, gonorrhoea, Ebola virus, brucellosis
Jaundice	Hepatitis, malaria, yellow fever, leptospirosis, relapsing fever
Lymphadenopathy	Rickettsial infections, brucellosis, dengue fever, HIV, Lassa fever, visceral leishmaniasis
Hepatomegaly	Amoebiasis, malaria, typhoid, hepatitis, leptospirosis
Splenomegaly	Malaria, relapsing fever, trypanosomiasis, typhoid, brucellosis, kala-azar, typhus, dengue fever
Eschar	Typhus, borrelia, Crimean-Congo haemorrhagic fever
Haemorrhage	Lassa, Marburg, or Ebola viruses; Crimean-Congo haemorrhagic fever; Rift valley fever; dengue; yellow fever; meningococcaemia; epidemic louse borne typhus; Rocky Mountain spotted fever

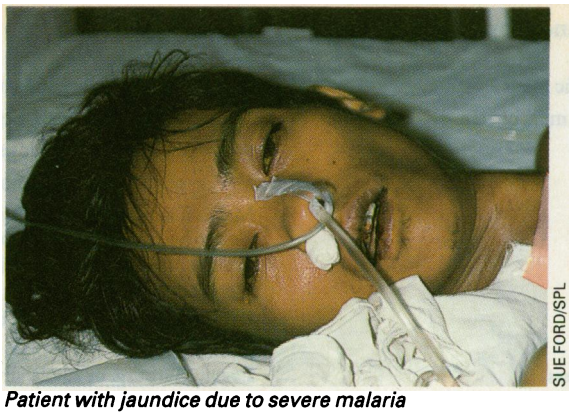
INVESTIGATION

Initial laboratory investigations for evaluating a febrile tropical illness should include a complete blood count with differential, thick and thin blood malaria films, liver function tests, cultures of blood and stool, urine analysis with urine culture, and, if suspected, serological tests for arboviral infections. Additional tests should be ordered on the basis of clues obtained from the history and physical examination. Although thick films for malaria are more sensitive for light infections, thin films are better for determination of species. Blood films should be repeated in 12-24 hours if the initial films are negative and malaria is suspected. Thrombocytopenia, although non-specific, is found in 50-80% of patients with malaria.[11,12] Eosinophilia is a characteristic finding in Katayama fever due to acute schistosomiasis; however, it may be unrelated to the febrile illness and be associated with a coexisting helminthic infection.[2,14] Liver function tests usually yield notably raised concentrations in hepatitis A, B, C, D, and E but also mild to moderately raised concentrations in Q fever, malaria, dengue fever, typhus, and typhoid fever as well as in numerous other systemic infectious diseases. In the first week of illness blood cultures are usually positive in typhoid fever and other enteric infections; in the second and subsequent weeks stool cultures become positive (as blood cultures become negative). Finally, it is often useful to store a tube of "acute" serum for antibody detection with a paired convalescent specimen at a later date.

Selected tropical infections

MALARIA

Imported malaria has become an increasing problem. About 90% of travellers from the tropics who have acquired malaria will not develop symptoms until after they have returned home.[18] Data on imported



Patient with jaundice due to severe malaria

infections show that in over 90% of cases, malaria due to *P falciparum* becomes symptomatic within two months of departure from an endemic area; malaria due to *P vivax*, on the other hand, is symptomatic in only 50% of cases during this period. Furthermore, a review of geographical areas in which malaria is acquired has shown that 90% of cases due to *P falciparum* originate from Africa and almost as many cases due to *P vivax* are acquired in Asia, particularly India.[11] Increasingly, malaria due to *P falciparum* has become drug resistant. As malaria may lead rapidly to death, it should be considered a medical emergency. Fever is almost always present; other manifestations include malaise, myalgias, headache, gastrointestinal complaints, and cough. Severe falciparum malaria may result in neurological deterioration, renal failure, and pulmonary oedema.[12] Diagnosis is based on the demonstration of parasites in thick and thin blood films. However, microscopic diagnosis and determination of species require a considerable skill that may be lacking in areas outside major referral centres; incorrect diagnosis is not uncommon in these settings.[19] Newer tests, such as the *Para*Sight®F assay based on antigen detection for diagnosis of *P falciparum* and the quantitative buffy coat (QBC®) method, may prove to be useful adjuncts to standard microscopy.[20,21]

DENGUE VIRUS AND OTHER ARBOVIRAL INFECTIONS

Dengue fever is the most common flavivirus infection of humans and is transmitted primarily by the day biting mosquito *Aedes aegypti*. Four serotypes of the dengue virus have been documented, and cross protective immunity after infection does not occur; subsequent infection with heterologous serotypes may be more severe.[16,17] Dengue fever typically has a short incubation period (usually one week or less) and presents with an abrupt onset of fever, chills, headache, retro-orbital pain, and severe myalgias, often with a transient macular rash. A secondary maculopapular rash characteristically appears between days 3 and 6. Lymphadenopathy and leukopenia may be present. Rarely, travellers may develop dengue shock syndrome or dengue haemorrhagic fever with thrombocytopenia, haemoconcentration, and haemorrhagic manifestations including purpura and gingival and gastrointestinal bleeding.[16,17] Epidemics of dengue fever have occurred throughout the tropics, but recently the emergence of dengue fever as a major public health problem has been most dramatic in Central and South America.[22] Diagnosis is based on clinical manifestations and can be confirmed by acute and convalescent arboviral serological tests. Treatment is primarily supportive.

ENTERIC FEVER

Enteric fever classically is caused by *Salmonella typhi* (typhoid fever), but a similar syndrome may be observed with *S paratyphi* and other salmonella serotypes. Infection is acquired by direct faecal-oral spread or by contaminated food or water.[13] Patients usually present after an incubation period of 3-60 days with a remittent fever pattern that becomes sustained. When malaria has been ruled out, enteric fever is the most common cause of fever lasting 10 or more days. Accompanying symptoms include headache, cough, and various gastrointestinal complaints, such as nausea, vomiting, and abdominal pain. Constipation is much more common than diarrhoea except in children.[13] Hepatosplenomegaly and rose spots may be present. Diagnosis is made by isolation of the organism in cultures of blood, stool, urine, or bone marrow. Quinolone antibiotics are the drugs of choice.[23]

RICKETTSIAL DISEASE

Although fever, headache, and myalgia in travellers returning from the tropics are non-specific, these symptoms may be due to a rickettsial illness such as tick typhus, scrub typhus, louse borne epidemic typhus, and Rocky Mountain spotted fever.[24] A maculopapular rash and regional lymphadenopathy often accompany the illness. Patients with tick and scrub typhus often have a painless eschar at the site of the insect bite. Diagnosis may be confirmed serologically, and appropriate treatment includes tetracycline or quinolone antibiotics.[25]

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